IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
DAVID **WALLACH,**
MARK BOLDIN, EUGENE VARFOLOMEEV, and
IGOR METT
Application No. 09/824,134
Filed: April 3, 2001

MODULATORS OF THE FUNCTION OF FAS/AP01 RECEPTORS

Examiner: Minh Tam B Davis
Art Unit: 1642

APPEAL BRIEF

Roger L. Browdy
Reg. No. 25,618
Attorney for Appellants
David Wallach et al

BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, D.C. 20001
Phone: 202-628-5197
Fax: 202-737-3528
Email: mail@browdyneimark.com

Attorney Docket: WALLACH16A

May 19, 2006

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Other Authorities

Rules

REAL PARTY IN INTEREST

The present application is owned by Yeda Research and Development Co. Ltd., which is the research and development arm of the Weizmann Institute of Science in Rehovot, Israel. The exclusive licensee of the present invention is Inter-Lab Limited, an Israeli company of Ness-Ziona, Israel. Inter-Lab Limited is a subsidiary of InterPharm Laboratories Limited, an Israeli company of Ness-Ziona, Israel, which is a member of the Serono group of companies, whose parent company is Serono S.A., a holding company under which there are many subsidiaries worldwide.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 1-7, 11 and 14 are pending in the present application and are subject to the present appeal. Claims 8-10, 12 and 13 have been cancelled.

STATUS OF AMENDMENTS

No amendment has been made subsequent to the most recent rejection of June 6, 2005, in this case. The Official action of June 6, 2005, was not a final rejection, although it is the fifth Official action on the merits issued in this case by the same examiner (without any intervening Request for Continued Examination). The last final rejection was dated March 4, 2004, and the claims have not been amended since that date.

SUMMARY OF CLAIMED SUBJECT MATTER

The only independent claim in this case is claim 1. No means plus function or step plus function as permitted by 35 U.S.C. §112, sixth paragraph, are present in claim 1.

Claim 1 is directed to an isolated DNA molecule as defined by any one of three alternative numbered paragraphs. Paragraph (1) of claim 1 is directed to the isolated DNA molecule comprising a DNA sequence that encodes the MORT-1 protein, having the amino acid sequence of SEQ ID NO:2. Thus, this portion of the claim is directed to any isolated DNA molecule that includes within it any DNA sequence that encodes the amino acid sequence of SEQ ID NO:2. The amino acid sequence of SEQ ID NO:2 is shown in Fig. 4. The protein having the amino acid sequence of SEQ ID NO:2 is defined in the specification as HF1 (see line 3 of the amended paragraph beginning at page 14, line 20, of the present specification). This novel protein is also known as MORT-1 (for "Mediator Of Receptor Toxicity"). See page 7, lines 19-20.

This paragraph of claim 1 covers not only the DNA sequence of the natural cDNA that encodes MORT-1, but also those sequences that are degenerate as a result of the genetic code to the cDNA sequence derived from the coding region of the native MORT-1 protein (see page 8, line 13-14). The claimed DNA sequence in paragraph 1 may be longer than the

sequence that encodes the MORT-1 protein so as to encompass, for example, vectors that contain the DNA sequence of the invention, but which also contain additional DNA regions that allow them to be capable of being expressed in suitable eukaryotic or prokaryotic host cells (see page 8, lines 24-27). Note that the sentence bridging pages 16 and 17 indicates that the MORT-1 protein may be conjugated to another molecule, for example an antibody, enzyme, receptor, etc., as are well known in the art. Note also the first paragraph on page 30, which refers to recombinant animal virus vectors encoding the MORT-1 protein, but which also encode a virus surface protein.

In paragraph (2) of claim 1, there is claimed an isolated DNA molecule comprising a DNA sequence that encodes an analog of the MORT-1 protein having the amino acid sequence of SEQ ID NO:2. This analog must bind with the intracellular domain of the FAS ligand receptor (FAS-IC). Furthermore, the DNA sequence which encodes that analog must be capable of hybridizing to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions. See page 8, lines 10-12. Note that while the isolated DNA molecule "comprises" the DNA sequence that encodes the analog of the MORT-1 protein, it is only the DNA sequence which encodes the analog that must be capable of

hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions.

The specification teaches that such analogs may be prepared by standard procedures, citing Sambrook et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (1989). See page 16, lines 5-6, and page 47, lines 1-2. In such procedures, the DNA sequences encoding the MORT-1 protein have one or more codons deleted, added or substituted by another to yield analogs having at least a one amino acid residue change with respect to the native protein (see page 16, lines 7-9). Acceptable analogs are those that retain at least the capability of binding to the intracellular domain of the FAS-R (see page 16, lines 9-10).

In paragraph (3) of claim 1, there is claimed an isolated DNA molecule comprising a DNA coding sequence consisting of a DNA sequence that encodes a fragment of the MORT-1 protein that binds with FAS-IC. The MORT-1 protein is that of the amino acid sequence of SEQ ID NO:2. See page 16, lines 20-28 of the present specification. Note that while the isolated DNA molecule "comprises" the DNA sequence that encodes a fragment of the MORT-1 protein, it is only the DNA sequence that encodes the fragment that must be capable of binding with FAS-IC.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the non-final rejection of June 6, 2005 (the fifth Official action on the merits in this case), claims 1-7, 11 and 14 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite in the language "moderately stringent conditions."

In the non-final rejection of June 6, 2005, claims 1-7, 11 and 14 were rejected under 35 U.S.C. §112, first paragraph, written description, with respect to lack of a clear written description of the claimed DNA sequence encoding an "analog" of the MORT-1 protein having the amino acid sequence of SEQ ID NO:2.

In the non-final rejection of June 6, 2005, claims 1-7, 11 and 14 were rejected under 35 U.S.C. §112, first paragraph, "scope," in that the specification lacks enablement for a DNA sequence encoding a fragment of MORT-1 protein that binds FAS-IC or encoding an "analog" of the MORT-1 protein having the amino acid sequence of SEQ ID NO:2.

ARGUMENT

Piecemeal Prosecution

It should be noted for the record that the prosecution of this case by the examiner (and it has been the same examiner throughout) has been extremely prejudicial to applicants as the examiner has resorted to piecemeal prosecution, which is not permitted by the Rules (see 37 C.F.R. §1.104). The first official action on the merits in this case was on October 23, 2002, and included rejections under 35 U.S.C. §112, second paragraph; 35 U.S.C. §112, first paragraph, written description; 35 U.S.C. §112, first paragraph, enablement; 35 U.S.C. §112, first paragraph, "scope;" 35 U.S.C. §102; and 35 U.S.C. §103. After a detailed response, a new non-final rejection was issued on July 3, 2003, inserting a new rejection under 35 U.S.C. §101 and maintaining only the 35 U.S.C. §112, first paragraph, written description, rejection and making a new rejection under 35 U.S.C. §112, first paragraph, enablement. The other rejections were apparently withdrawn in view of applicants' arguments.

After a further detailed response by applicants, the examiner issued a final rejection on March 4, 2004, objecting only to the second paragraph of claim 1 under 35 U.S.C. §112, first paragraph, enablement. After that, an Appeal Brief was

filed, after which a new non-final rejection was issued on February 25, 2005, containing only a double-patenting rejection. The previous enablement rejection was not repeated. Thus, applicants were under the impression that, if the double-patenting rejection were overcome, the case would be in condition for allowance. However, on June 6, 2005, a fifth non-final Official action was issued by the examiner re-inserting the 35 U.S.C. §112, second paragraph, rejection from the official action of October 23, 2002; re-inserting the 35 U.S.C. §112, first paragraph, written description rejection, from the official action of July 3, 2003; and re-inserting the 35 U.S.C. §112, first paragraph, rejection from the official action of March 4, 2004, all of which had been previously withdrawn by the examiner.

While this inappropriate piecemeal prosecution by the examiner is not appealable, we feel it important enough to bring to the Board's attention as it may affect the weight to be given to the examiner's case.

The Language "Under Moderately Stringent Conditions" Is Not Unduly Vague and Indefinite

The language "under moderately stringent conditions" is not unduly vague and indefinite. MPEP §2173.02 states:

> The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph, is whether the claim meets the

> threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. ...
>
> The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) the content of the particular application disclosure;
>
> (B) the teachings of the prior art; and
>
> (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

At the time the present invention was made, the metes and bounds of moderate stringency were known to those of skill in the art, even though there may be some variation in the means for providing roughly the same level of stringency either at the hybridization stage or at the wash stage. U.S. patent 5,026,636, relevant pages of which are attached in the Evidence Appendix, was available at the time the invention was made and defines moderate stringency as conditions that allow detection of nucleotide sequences at least approximately 75% homologous to the probe (column 4, lines 50-65). This patent further teaches that moderately stringent conditions for a particular probe, when seeking a specified degree of homology, may be readily determined by those of skill in the art using,

for example, the reference text, Nucleic Acid Hybridisation: A Practical Approach, Hames and Higgins, eds., IRL Press, Washington (1985) or the scientific publication, Wood et al, Proc Natl Acad Sci USA 82:1585-1588 (1985) (copy of which is attached hereto in the Evidence Appendix), for guidance. Chapter 4 of Nucleic Acid Hybridisation: A Practical Approach, on quantitative filter hybridization, a copy of which is attached hereto in the Evidence Appendix, teaches the various factors affecting hybrid stability through a calculation of melting temperature (T_m) of the hybrid using the standard equation (Equation 7 on page 80) and factoring in the percent mismatch (percent identity) that is sought. The calculation of T_m takes into account the molarity of the monovalent cation (i.e., sodium in SSC solution). Accordingly, those of skill in the art would recognize and understand what the metes and bounds of the conditions needed for moderate stringency hybridization to detect a hybrid with a specified percent identity, e.g., 75%.

Indeed, U.S. patents 4,968,607 (50°C, 2 X SSC; column 10, lines 39-40), 5,171,675 (50°C, 2 X SSC; column 6, line 49), 5,198,342 (50°C, 2 X SSC; column 9, lines 54-55), 5,262,522 (50°C, 2 X SSC; column 15, lines 8-9), and 5,237,051 (60°C, 1 X SSC; column 5, lines 24-27), which were available to the art at the time of the present invention, demonstrate

that those in the art were able to determine and define moderately stringent conditions based on the knowledge and skill at that time. All have claims that include the term "moderate stringency". Relevant pages of the above-cited U.S. Patents are attached hereto in the Evidence Appendix. According to the Federal Circuit Court of Appeals, it is relevant to the issue of definiteness that the criticized words are used frequently in patent claims. See *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 USPQ2d 2010, 2012-13 (Fed. Cir. 1988). And see also *Ex parte Brian*, 118 USPQ 242, 245 (Bd. App. 1958), where it states:

> Since the claims under consideration are similar to those in the patents, we do not feel disposed to reject them and thus upset such a long established practice in the particular art under consideration.

In other words, the very fact that "moderate stringency" claims have been repeatedly allowed in the past is reason to consider them definite. This is true, not only because the use of such claims by many different inventors and allowed by many different examiners is evidence that the terminology is considered sufficiently definite by the art, but also because a reinterpretation of the definiteness of such claims by the PTO casts a shadow of doubt on previously issued "moderate stringency" claims, even though such claims are entitled to a presumption of validity.

Furthermore, the widely used reference text, Current Protocols in Molecular Biology, eds. Ausubel et al, John Wiley & Sons, Inc., (1987-1998) on page 2.10.11 (Supplement 26, 1994[1]), a copy of which is also attached in the Evidence Appendix, guides those of skill in the art how to use a rational approach at determining "moderate stringency" wash conditions by calculating the decrease in temperature required using the correlation for decrease in T_m per percent mismatch.

Accordingly, in view of the teachings of the prior art, it is urged that the claim interpretation to be given to the term "hybridization under moderately stringent conditions" are those conditions which would permit detection of nucleotide sequences at least approximately 75% homologous. Thus, the scope of the invention sought to be patented can be determined from the language of the claims with a reasonable degree of certainty.

The examiner does not consider the substantial citation of evidence by applicants in this regard to be convincing to show that one of ordinary skill in the art would consider the term "moderately stringent conditions" to be reasonably definite. The examiner states that there is no definition of "moderately stringent hybridization conditions"

[1] A copy of page 2.6.1 is also attached in the Evidence Appendix that shows that Supplement 26 is dated 1994).

found in the specification. The examiner concedes that some U.S. patents use the language or define the language, and some references teach how to determine moderate stringency wash. However, the examiner states that the definition by another U.S. patent would be just one of numerous possible reasonable interpretations of the claimed moderately stringent hybridization conditions in view of the lack of definition of the term in the claimed application and in view of the fact that "moderate" is a relative term.

It is noted, however, that the examiner has not cited any reference to show that one of ordinary skill in the art would consider the term to be other than what applicants have established. As stated in *In re Barr*, 444 F.2d 588, 170 USPQ 330 (CCPA 1971), to answer the question of whether the claims fail in particularly pointing out and distinctly claiming the subject matter that appellants regard as their invention, the claims must be construed from the standpoint of a person skilled in the relevant art. See also paragraph (C) in the above-quoted section of MPEP §2173.02. Claim interpretation during prosecution is explained at MPEP §2111, which states that claims must be given their broadest reasonable interpretation consistent with the interpretation that those skilled in the art would reach. This section of

the MPEP cites *In re Cortright*, 175 F.3d 1353, 1358, 49 USPQ2d 1464, 1467 (Fed Cir 1999), which case states:

> Although the PTO must give claims their broadest reasonable interpretation, this interpretation must be consistent with the one that those skilled in the art would reach. ... Prior art references may be "indicative of what all those skilled in the art generally believe a certain term means ... [and] can often help to demonstrate how a disputed term is used by those skilled in the art." *Vigronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1584, 39 USPQ2d 1573, 1578-1579 (Fed. Cir. 1996)*. Accordingly, the PTO's interpretation of claim terms should not be so broad that it conflicts with the meaning given to identical terms in other patents from analogous art. Cf. [*In re Morris*, 127 F.3d 1048, 1056, 44 USPQ2d 1023, 1029 (Fed. Cir. 1997)] (approving the board's definition of claim terms consistent with their definitions in CCPA cases).

Thus, it is permissible to consider how similar language is defined and interpreted in other patents.

As to the examiner's complaint that the term "moderate" is a relative term, reference is made to MPEP §2173.05(b), which states:

> The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. §112, second paragraph. ... Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification.
>
> As stated at MPEP §2173.02:
>
> When the examiner is satisfied that patentable subject matter is disclosed, and

> it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. [emphasis original]

Here, there is no rejection over the prior art. The examiner is satisfied that the subject matter is patentable over the prior art. Accordingly, the language "moderately stringent conditions," considered in light of the evidence presented herein as to how that term would be construed by one of ordinary skill in the art when giving the present specification its broadest reasonable interpretation, should establish that the patentable subject matter is defined with a reasonable degree of particularity and distinctness.

Indeed, these very arguments were found convincing to this same examiner when presented in applicants' amendment of February 24, 2003. Accordingly, the examiner's reasons for re-inserting the rejection, notwithstanding three intervening Official actions that did not re-insert it, should be given very little weight.

Reversal of the examiner and withdrawal of this rejection are therefore respectfully urged.

The Specification Establishes that Applicants Were in Possession of the Claimed Invention

It is apparent that this written description rejection only applies to the second paragraph of claim 1, which uses the term "analog." This part of the claim makes clear that it is the analog that must bind with the intracellular domain of the FAS ligand receptor (FAS-IC). Thus, the claim includes the function of binding to FAS-IC. Further, this paragraph states that the DNA sequence is capable of hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions. Thus, this part of the paragraph defines the sequence by structure.

The Guidelines for the Examination of Patent Applications under the 35 U.S.C. §112, paragraph 1, "Written Description" Requirement, as set forth in MPEP §2163, states at II.A.3.(a):

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem,* [*Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002)].

Here, the analog of claim 1(2) is defined by a complete or partial structure and other physical and/or chemical properties. The examiner concedes that binding is a physical property. There is effectively a partial structure because the DNA encoding it must be capable of hybridizing to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions. Thus, this combination of partial structure and physical and/or chemical properties is sufficient to show that applicant was in possession of the claimed invention.

Binding alone is sufficient to establish the function of serving in affinity chromatography to isolate FAS-IC protein. Note that the affinity chromatography function is mentioned, for example, at page 21, lines 5-9, where it states that affinity chromatography may be used to characterize additional proteins, factors, receptors, etc., which are capable of binding to the MORT-1 protein of the invention. This, of course, includes FAS-IC, as is stated in the following two lines. Accordingly, the present claims fully satisfy the written description guidelines, as it is perfectly acceptable to show that one is in possession of a compound by identifying characteristics that include physical properties.

As to the question of whether or not the full scope of presently-claimed analogs is supported by a sufficient written description in view of the fact that only a single species is

disclosed in the specification, reference is made to the Revised Interim Written Description Guidelines Training Materials (a copy that has recently been downloaded from the PTO website being attached hereto in the Evidence Appendix), Example 14: "Product-by-Function," beginning on numbered page 53 of the attached copy. In that example, the specification exemplified a protein isolated from liver that catalyzed the reaction of A→B, which isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO:3. The specification also contemplated, but did not exemplify, variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions, and additions. The specification indicated that procedures for making proteins with substitutions, deletions, insertions, and additions is routine in the art and provided an assay for detecting the catalytic activity of the protein.

This description in the specification is very similar to the description that appears in the present specification. The present specification exemplifies a MORT protein that binds FAS-IC. The sequence of this protein is specified. The specification contemplates, but does not exemplify, analogs of the protein wherein the variant is encoded by a DNA molecule that hybridizes to the MORT-1 encoding DNA molecule under moderately stringent hybridization conditions. The present specification also indicates that procedures for making such analogs, including by

modification of the DNA sequences encoding them, are routine in the art (see, for example, page 16, lines 5-9) and provides an assay for determining whether any given protein binds to FAS-IC. See, for example, page 34, lines 3-13.

In Example 14 of the Training Materials, the claim is directed to:

> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B.

The analysis in the Training Materials acknowledges that procedures for making variants of SEQ ID NO:3 are conventional in the art and that an assay is described which will identify other proteins having the claimed functionality. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity were conceded as being conventional in the art. It would, of course, be understood that procedures for making analogs (variants) of the polypeptide of paragraph (1) of claim 1, which analogs are as defined in paragraph (2) of claim 1, are also conventional in the art.

The analysis goes on to point out that all variants of the claim must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO:3. Furthermore, because of the "having" language, the protein claimed may be larger than SEQ ID NO:3 or its variant with 95% identity to SEQ ID NO:3. The analysis points out that the specification contains a

reduction to practice of the single disclosed species. The analysis concludes at pages 54-55:

> The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> Conclusion: The disclosure meets the requirements of 35 USC §112, first paragraph, as providing adequate written description for the claimed invention.

Thus, it is apparent that if the single species disclosed is representative of the genus and an assay is present for identifying the members of the variants that are capable of the specified functionality, the written description requirement is met. Here, the requirement of moderately stringent hybridization conditions and the disclosure of the assay also are sufficient to identify all of the analogs that are capable of the specified binding activity. As in the example, one of skill in the art would conclude applicants were in possession of the necessary common structure possessed by the members of the genus despite disclaimers of only a single species.

It should further be noted that it is not uncommon to claim analogs by such hybridization language. In this regard, reference is made to Example 9, "Hybridization," in the same Training Materials, beginning at numbered page 35. In that example, the following claim was analyzed for compliance with the written description requirement of 35 U.S.C. §112:

> An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

The result of this analysis was that the claimed invention is adequately described. As the polypeptide encoded by any such nucleic acid hybridizing under the specified conditions can readily be tested without undue experimentation for ability to block cell proliferation, the experimentation needed to practice the invention was found not undue or unreasonable.

As the Training Materials acknowledge that hybridization language can be acceptable and that a genus of analogs can be claimed based on the disclosure of only a single member of that genus, the situation in this case would warrant a similar analysis, whereby the analogs defined in paragraph (2) of claim 1 are considered to be supported by the written description of the present specification.

The examiner points to the disclosure at page 6, lines 4-5 of the present specification that a certain fragment of MORT-1 does not bind to the MORT-1 protein of SEQ ID NO:2, but does bind to FAS-IC. The examiner states that this could not be used for making an affinity column to isolate MORT-1 protein. If, by inadvertent error in a previous paper in the prosecution of this application, applicants referred to an affinity column to isolate "MORT-1 protein," this error is regretted. It is clear, however, that the claimed function is binding to FAS-IC, and the reference to an affinity column at page 21, lines 5-9, of the present specification can equally apply to the isolation of FAS-IC as an additional protein or receptor that binds to MORT-1 protein. Furthermore, the fact that there may be fractions of SEQ ID NO:2 that do not bind to FAS-IC is irrelevant as the claim requires binding to FAS-IC, and the assay described in the present specification establishes that only those sequences that do bind to FAS-IC are within the scope of the claim.

The examiner states that binding to FAS-IC alone is not a definitive function. However, this is not understood. It is an important function as it allows FAS-IC to be isolated by affinity chromatography. It is definitive as it is easy to determine whether any given analog of MORT-1 has such binding capability.

The examiner states that there is no correlation provided between the function of binding to FAS-IC and the

structure of proteins encoded by DNA sequence having the ability to hybridize to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions. However, such a correlation is not necessary in view of the fact that it would not take undue experimentation to subject the proteins that are encoded by the DNA that binds under moderately stringent conditions to a simple binding assay to determine which of those bind to FAS-IC.

As indicated above, those of ordinary skill in the art understand that to bind under moderately stringent conditions, such a DNA would have to have at least about 75% homology. This is a sufficiently defined structure.

For all of these reasons, reversal of the examiner and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, written description, are respectfully urged. It is further urged that the fact that this rejection was withdrawn in the official action of March 4, 2004, and was not re-inserted in the official action of February 25, 2005, and only reinstated on June 6, 2005, diminishes the gravitas of the examiner's argument and the relative arguments should be weighed accordingly.

Determining Which Analogs Bind FAS-IC Would Not Entail Undue Experimentation

The examiner states that applicants have not taught how to make variants that are capable of hybridizing to the cDNA encoding SEQ ID NO:2 under moderately stringent

conditions, such that those variants would bind with the intracellular domain of the FAS ligand receptor (FAS-IC). The examiner states that one would not know how to make the claimed variants in view of a lack of adequate teaching in the specification, and in view of the unpredictability of protein chemistry and the DNA sequences that encode proteins.

The examiner's argument fails in view of the fact that it is not necessary to know in advance which variants of the cDNA encoding SEQ ID NO:2 would bind with FAS-IC. It is not necessary to decide whether protein chemistry is predictable or unpredictable. The point is that mutations in the cDNA can be randomly made with all of the random mutations being tested *en masse* for hybridization under moderately stringent conditions. The same is true for fragments of SEQ ID NO:2. All those that hybridize can then be cloned so as to produce an expression product of the DNA in question, and that expression product tested by a very simple binding assay to determine if it binds to the intracellular domain of FAS (FAS-IC). Whatever is found to hybridize under moderately stringent conditions and to encode a polypeptide that binds to the FAS-IC falls within the scope of the claim. Anything else does not. None of these steps involve undue experimentation.

The specification at page 16 cites Sambrook et al (1989) for standard procedures to prepare analogs. Among such

standard procedures are treatment of double-stranded DNA with chemical mutagens, treatment of single-stranded DNA with sodium bisulfite, and treatment of single-stranded DNA with chemicals that damage all four bases, which appear at pages 15.105-15.107 of the Sambrook reference. These are all procedures that would have been well known to those of ordinary skill in the art at the time of the effective filing date of the present application. Simple *in vitro* binding assays are described, for example, at page 34, lines 3-13, of the specification.

The amount of experimentation that may be permitted in order to satisfy the enablement requirement of 35 U.S.C. §112 is discussed in *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In this regard, *Wands* states, 858 F.2d at 736-737, 8 USPQ2d at 1404:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "The key word is 'undue,' not 'experimentation.'"
>
> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878-879; 169 USPQ 759, 762-763 (2d Cir. 1971), *cert. denied,* 404 U.S. 1018, 30 L. Ed. 2d 666, 92 S. Ct 680 (1972)]. The test is not merely quantitative, since a

> considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed***.
>
> [Footnotes omitted - the latter quote being from *In re Jackson*, 217 USPQ 804, 807 (Bd. App. 1982)]

Wands goes on to state, 858 F.2d at 737, 8 USPQ2d at 1404:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [Footnotes omitted]

In analyzing these factors in this case, the conclusion must be reached that the experimentation is not undue. As to the first factor, the quantity of experimentation may be significant, as random mutations would have to be generated, hybridization experiments conducted, and screening conducted of those that are found to hybridize under moderately stringent conditions using a simple binding assay. However, in the *Wands* case, it was found that routine screening does not necessarily amount to undue experimentation.

With respect to the second factor, the amount of guidance or direction presented, the specification refers to the Sambrook reference, which is the laboratory manual used by everyone of ordinary skill in this art. Everything in it is known and within the skill of those of ordinary skill in the art. Less guidance is needed for well-known techniques. Substantial guidance as to a specific binding screen is provided at page 34.

As to the third factor, the presence or absence of working examples, the binding assay at page 34 is sufficiently detailed to serve as a working example.

As to the fourth factor, the nature of the invention, the nature of the invention is such that substantial experimentation is acceptable. As will be discussed in the following factors, the field of this invention requires a very high level of skill in the art, and practitioners are well inured to screening that takes substantial experimentation quantitatively.

As to the fifth factor, the state of the prior art, moderate stringency hybridization, random mutagenesis and binding assays are all well-documented in the prior art. The examiner has not doubted this fact, and so it has not been necessary to submit evidence proving it. The present invention does not involve any of these specific techniques

per se. Their use on the novel DNA sequence of the present invention is the advance made by the present inventors.

As to the sixth factor, the relative skill of those in the art, those of ordinary skill in the art of recombinant DNA technology is very high, usually requiring a Ph.D. and/or substantial laboratory experience. For such persons, a greater amount of experimentation would be considered to be routine than for technologies requiring a lower level of skill in the art.

As to the seventh factor, the predictability of the art, predictability is not relevant here, as no predictability is necessary. One need only do the experiments and screen; the results will provide all of the answers. It is not necessary to predict the answers in advance.

As to the eighth factor, the breadth of the claims, paragraph 2 of claim 1 is not so broad so as to require undue experimentation to find what would fall within it for the reasons as discussed above with respect to all of the other factors.

Accordingly, as in *In re Wands*, analysis of the facts of the present case, considering the factors enumerated in *Ex parte Forman*, leads to the conclusion that undue experimentation would not be required to practice the invention. There was a high level of skill in the art at the time when the application

was filed and all of the methods needed to practice the invention were well known.

The examiner states that applicants have not taught how to make variants that are capable of hybridizing to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions such that those variants would have the properties and function of the claimed polynucleotides encoding SEQ ID NO:2. However, this is not required by the present claims. The present claims only require that the variants bind to the intracellular domain of the FAS ligand receptor. The examiner states that not everything that binds to the FAS-IC receptor will cause the receptor to be activated. However, nothing in the claim requires activation of the FAS-IC receptor or any other activity *in vivo*. The claim only requires that the polypeptide encoded by the DNA that binds to SEQ ID NO:2 under moderately stringent conditions bind to FAS-IC. The specification discloses that binding to FAS-IC has a separate *in vitro* utility in affinity chromatography. A protein that binds to FAS-IC can be used to isolate FAS-IC or the FAS receptor by affinity chromatography, and this is a valid utility. A claim needs only be supported by a single utility. The examiner's comments about whether or not the protein can be used to activate the FAS receptor or otherwise have all of the other properties of MORT-1 are irrelevant. The name of the game is the claim. The claim does not require such activation.

It is noted that the examiner has not rebutted the *Wands* analysis made in the previous filing of the Brief and repeated herein. Further, the examiner has conceded that one could screen for fragments of SEQ ID NO:2 that bind to FAS-IC (see the first sentence of the last paragraph on page 9 of the official action of June 6, 2005).

It should again be noted that following the filing of a Appeal Brief in this case on December 6, 2004, the examiner issued an Official action on February 25, 2005, in which the enablement rejection was not repeated. Accordingly, the examiner was at one point convinced by applicants' arguments. The fact that the examiner in a fifth Official action on the merits should reinstate a rejection despite arguments that were previously found convincing should affect the weight that the Board gives to the examiner's arguments in a negative fashion.

For all of these reasons, reversal of the examiner and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, enablement, are respectfully urged.

CONCLUSION

The claims as submitted are believed to truly set forth the inventive concept of the present invention and to fully comply with the written description and enablement requirements of the first paragraph of 35 U.S.C. §112 and the definiteness requirement of the second paragraph of 35 U.S.C. §112. Accordingly, reversal of the examiner and allowance of claims 1-7, 11 and 14 are earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /rlb/
Roger L. Browdy
Registration No. 25,618

RLB:rd
G:\BN\I\inl2\Wallach16A\Pto\AppealBrief2.doc

CLAIMS APPENDIX

This listing of claims includes all of the claims involved in the appeal.

Listing of Claims:

1. An isolated DNA molecule comprising:

(1) a DNA sequence which encodes the MORT-1 protein, having the amino acid sequence of SEQ ID NO:2;

(2) a DNA sequence which encodes an analog of said MORT-1 protein, which analog binds with the intracellular domain of the FAS ligand receptor (FAS-IC), which DNA sequence is capable of hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions; or

(3) a DNA coding sequence consisting of a DNA sequence which encodes a fragment of said MORT-1 protein which binds with FAS-IC.

2. An isolated DNA molecule in accordance with claim 1, comprising a DNA sequence encoding an analog of said MORT-1 protein which binds with FAS-IC, which DNA sequence is capable of hybridization to the cDNA encoding SEQ ID NO:2 under moderately stringent conditions.

3. A vector comprising a DNA sequence according to claim 1.

4. A vector according to claim 3 which is capable of being expressed in a eukaryotic host cell.

5. A vector according to claim 3 which is capable of being expressed in a prokaryotic host cell.

6. Isolated transformed eukaryotic or prokaryotic host cells containing a vector according to claim 3.

7. A method for producing a polypeptide which binds to the intracellular domain of the FAS-R, comprising growing the isolated transformed host cells according to claim 6 under conditions suitable for the expression of an expression product from said cells, effecting post-translational modifications of said expression product as necessary for obtention of said polypeptide, and isolating said expressed polypeptide.

8-10 (Cancelled).

11. A recombinant animal virus vector encoding a virus surface protein capable of binding a specific target cell surface receptor and further including the sequence of a DNA molecule of claim 1.

12-13 (Cancelled).

14. An isolated DNA molecule in accordance with claim 1 wherein the entire said DNA sequence is a coding sequence encoding said polypeptide.

EVIDENCE APPENDIX

U.S. Patent 5,026,636: Amendment of February 24, 2003, for example, at page 7; such amendment was entered and considered in the next official action on July 3, 2003.

Wood et al, Proc Natl Acad Sci USA 82:1585-1588 (1985): Amendment of February 24, 2003, for example, at page 7; such amendment was entered and considered in the next official action on July 3, 2003.

Hames and Higgins (eds.), Nucleic Acid Hybridisation: A Practical Approach, Chapter 4, IRL Press, Washington (1985): Amendment of February 24, 2003, for example, at pages 7-8; such amendment was entered and considered in the next official action on July 3, 2003.

U.S. Patent 4,968,607: Amendment of February 24, 2003, for example, at page 8; such amendment was entered and considered in the next official action on July 3, 2003.

U.S. Patent 5,171,675: Amendment of February 24, 2003, for example, at page 8; such amendment was entered and considered in the next official action on July 3, 2003.

U.S. Patent 5,198,342: Amendment of February 24, 2003, for example, at page 8; such amendment was entered and considered in the next official action on July 3, 2003.

U.S. Patent 5,262,522: Amendment of February 24, 2003, for example, at page 8; such amendment was entered and considered in the next official action on July 3, 2003.

U.S. Patent 5,237,051: Amendment of February 24, 2003, for example, at page 8; such amendment was entered and considered in the next official action on July 3, 2003.

Ausubel et al (eds.) Current Protocols in Molecular Biology, eds. John Wiley & Sons, Inc., (1987-1998) on page 2.10.11 (Supplement 26, 1994) (including a copy of page 2.6.1 that shows that Supplement 26 is dated 1994): Amendment of February 24, 2003, for example, at page 9; such amendment was entered and considered in the next official action on July 3, 2003.

Revised Interim Written Description Guidelines Training Materials: This is being provided as a citation of authority that may not be readily available to the Board members.

RELATED PROCEEDINGS APPENDIX

None